PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
GOWLING LAFLEUR HENDERSON LLP
2600 - 160 Elgin Street
OTTAWA, Ontario
Canada, K1P 1C3

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	11 May 2005 (11-05-2005)
Applicant's or agent's file reference 08899427WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2005/000025	10 January 2005 (10-01-2005)	09 January 2004 (09-01-2004)

International Patent Classification (IPC) or both national classification and IPC
IPC(7): C12N-15/11, C07K-7/06, C07K-16/16, A23L-1/29, C07K-14/415, C12N-15/29, G01N-33/02, G01N-33/48, G01N-33/564

Applicant
OTTAWA HEALTH RESEARCH INSTITUTE ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[X]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[X]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[X]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA	Date of completion of this opinion	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	26 April 2005 (26-04-2005)	Michael W. De Vouge (819) 997-2952

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   [X] the international application in the language in which it was filed

   [ ] a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :

   a. type of material

      [X] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of material

      [X] on paper

      [X] in electronic form

   c. time of filing/furnishing

      [X] contained in the international application as filed.

      [X] filed together with the international application in electronic form

      [ ] furnished subsequently to this Authority for the purposes of search.

3 [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

Box No. II Priority

1. [ ] The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.

2. [ ] This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

The priority document was not available to the examiner for review. Therefore, the priority date was considered valid for the establishment of the Written Opinion.

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

[ ] the entire international application

[X] claim Nos. 8, 12, 13, 21, 24, 25

because:

[ ] the said international application, or the said claim Nos. relate to the following subject matter which does not require an international search *(specify)* :

[X] the description, claims or drawings *(indicate particular elements below)* or said claim Nos. 8, 12, 13, 21, 24, 25 are so unclear that no meaningful opinion could be formed *(specify)* :

Polypeptides and nucleotide sequences of claims 8, 12, 13, 21, 24 and 25 are defined by functional rather than structural attributes, thus rendering it impossible to undertake a meaningful search over their entire scope. The application provides sufficient clarity under Article 6 (PCT) and sufficiency of disclosure under Article 5 (PCT) for only a limited number of claimed embodiments. Consequently, the search has been restricted to claims of amino acid sequences, nucleotide sequences that encode said amino acid sequences, antibodies and kits that are derived from gliadin isoforms or gbl1(wheat storage globulin).

[ ] the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify):*

[ ] no international search report has been established for said claims Nos.

[ ] a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

[ ] furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

[ ] furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

[ ] pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

[ ] a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

Box No. IV Lack of unity of invention

1. [X] In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit :

   [ ] paid additional fees

   [ ] paid additional fees under protest and, where applicable, the protest fee

   [ ] paid additional fees under protest but the applicable protest fee was not paid

   [X] not paid additional fees

2. [ ] This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   [ ] complied with

   [X] not complied with for the following reasons :

   The International Search authority found multiple groups of inventions in this international application, as follows:

   I. Claims 1-25:
   Amino acid sequences comprising diabetogenic epitopes, nucleotide sequences encoding such epitopes, antibodies reactive with such epitopes, and kits.

   II. Claims 26 and 27:
   Method of screening foodstuffs to identify immunogenic proteins therewithin.

   III. Claims 28-32:
   Foodstuffs modified to reduce or eliminate diabetogenic epitopes.

   IV. Claims 33-35:
   Method of screening a subject for reactivity toward food proteins.

   The special technical feature linking claims of Invention I is considered to be the identification of diabetogenic epitopes, in particular those from gliadin and gbl1. Claims of Inventions II and IV are held to be distinct from Invention I in that the claimed methods as recited are generic and do not utilize or exploit said special technical feature. Claims of Invention III are held to be distinct from those of Invention I in that the claimed products of each invention are structurally dissimilar and fail to share said special technical feature.

4. Consequently, this opinion has been established in respect of the following parts of the international application :

   [ ] all parts

   [X] the parts relating to claim Nos. 1-25

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2, 7, 15, 16, 23	YES
	Claims	1, 3-6, 8-14, 17-22, 24, 25	NO
Inventive step (IS)	Claims	2, 7, 15, 16, 23	YES
	Claims	1, 3-6, 8-14, 17-22, 24, 25	NO
Industrial applicability (IA)	Claims	1-25	YES
	Claims	None	NO

2. Citations and explanations :

Reference is made to the following documents:
D1 - OKITA et al, J Biol Chem 260(13): 8203-8213, 1985 (July 5)
D2 - LITTS et al, GenBank nucleotide sequence database, accession no. M81719, 1993 (27 Apr)
D3 - OSMAN et al, Eur J Gastroenterol Hepatol 13(10): 1189-1193, 2001 (Oct)
D4 - GIL GARCIA et al, Hybrid Hybridomics 22(6): 383-388, 2003 (Dec)
D5 - WO01/25793 A2 (ISIS INNOVATION (GB)) 12 April 2001

With regard to novelty and inventive step:

Claims 1, 3, 6 and 8-12 are not considered to meet the requirements of Articles 33(2) or 33(3) PCT for novelty or inventive step, in view of each of documents D1 or D2. Document D1 discloses amino acid and nucleotide sequences of α-/β-type and γ-type gliadin isoforms. Document D2 discloses the nucleotide sequence and amino acid sequence of the *Triticum aestivum* wheat storage globulin gene (gbl1). Because functional attributes such as diabetogenic epitopes are considered to be an inherent property of the gliadin and gbl1 amino acid sequences, it is held that the instant claims would encompass gliadin and gbl1 polypeptides and nucleotide sequences already known from the art. The discovery that gliadin and gbl1 contain diabetogenic epitopes would not confer novelty on the known proteins or nucleotide sequences (including complement) encoding such proteins. The nucleotide sequences isolated would necessarily have been associated with cloning vectors having regulatory sequences during the course of their analysis. Thus, each of the sequences of documents D1 and D2 are held to anticipate those of the instant claims. Consequently, the instant claims are considered to lack both novelty and an inventive step.

Claims 14 and 17-20 are not considered to meet the requirements of Articles 33(2) or 33(3) PCT for novelty or inventive step, in view of either of documents D3 or D4. Each of said documents disclose the production of monoclonal antibodies directed against epitopes of gliadins, and thus constitute isolated antibodies capable of binding to one or more isoforms of gliadin proteins. With regard to claim 20, the recitation that a serum is produced in a diabetic animal is not held to confer novelty on the antibodies of claim 14, as ability to produce an antibody directed against gliadins or gbl1 would not necessarily be influenced by the diabetic condition of said animal. Thus, the cited art is held to anticipate the instant claims. Consequently, the instant claims are considered to lack both novelty and an inventive step.

...continued in Supplemental Box

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted :

In claim 7, "diabetogeic" should be spelled as "diabetogenic";

throughout the description and claims, the wheat storage globulin gene is designated as "glb1" rather than the accepted designation known in the art "gbl1".

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

The scope of claims 8, 12, 13, 21, 24 and 25 renders it impossible to undertake a meaningful search over their entire scope, as the polypeptides and nucleotide sequences are defined by functional rather than structural attributes. As such, the application provides sufficient clarity under Article 6 (PCT) and sufficiency of disclosure under Article 5 (PCT) for only a limited number of claimed embodiments. Consequently, the search has been restricted to amino acid sequences, nucleotide sequences that encode said amino acid sequences, antibodies and kits that are derived from gliadin isoforms or gbl1 (wheat storage globulin).

Claims 1, 3-6, 8-14, 17-22, 24 and 25 are not considered to meet the requirements of Article 5 (PCT) with regard to diabetogenic epitopes of gliadin or antibodies directed against such epitopes, as the instant description discloses clones encoding gliadin isoforms, but fails to identify any regions by sequence that would constitute a diabetogenic epitope. Thus, the description is held to be insufficient to enable a skilled artisan to practice the invention.

Claims 1-25 are not considered to meet the requirements of Article 6 (PCT) with regard to diabetogenic epitopes of gbl1, as the scope of said claims exceeds that disclosed within the instant description. Specifically, said description discloses a clone WP5212 that comprises a sequence encoding a diabetogenic epitope EEQLRELRRQ, but which exhibits 90% nucleotide sequence identity to the wheat storage globulin gbl1. Thus, it is unclear whether clone WP5212 actually encodes a wheat storage globulin, and whether said epitope may be characteristic of wheat storage globulins in general.

Claim 1 is not considered to meet the requirements of Article 6 (PCT) for clarity, as the gene recited by the designation "glb1" is not fully identified. It is also noteworthy that the designation is different from that (gbl1) which is commonly known in the art.

Claim 3 is not considered to meet the requirements of Article 6 (PCT). The phrase "that does not occur naturally in nature" is ambiguous, as it is uncertain whether or not this phrase applies to synthesized peptides, or enzyme-digested fragments of a protein.

Claims 8, 21 and 24 are not considered to meet the requirements of Article 6 (PCT) for clarity, as recited portions of sequences or kit components are not restricted by a minimum effective size.

Claim 9 is not considered to meet the requirements of Article 6 (PCT) for clarity, as the phrase "comprising part of a larger nucleotide sequence" introduces ambiguity into the claimed subject matter, as the claim now recites a nucleotide sequence of claim 6 that includes part of a larger nucleotide sequence without identifying said larger sequence or what proportion of said larger sequence is included in the nucleotide sequence of claim 6.

Claims 10 and 11 are not considered to meet the requirements of Article 6 (PCT) for clarity, as the scope of the claimed subject matter exceeds that of the claim on which it depends. Claim 10 is directed to a larger nucleotide sequence of claim 9, whereas claim 9 is directed to a nucleotide sequence of claim 6 encoding a diabetogenic epitope from gbl1 or gliadin. The larger nucleotide sequence is held to extend outside the subject matter of claim 6.

Claim 13 is not considered to meet the requirements of Article 6 (PCT) for clarity, as the scope of the claimed subject matter exceeds that of the claim on which it depends. Claim 13 is directed to a larger nucleotide sequence of claim 12, whereas claim 12 is directed to a nucleotide sequence of claim 8 that is complementary to a nucleotide sequence encoding a diabetogenic epitope. The larger nucleotide sequence is held to extend outside the subject matter of claim 8.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: Box V

Claims 1, 3-6, 8-14, 17-22, 24 and 25 are not considered to meet the requirements of Articles 33(2) or 33(3) PCT for novelty or inventive step, in view of document D5. Document D5 discloses a nucleotide sequence of A-gliadin (SEQ ID NO:3) in cloning and/or expression vectors, the amino acid sequence thereof, peptides comprising T-cell epitopes thereof, antibodies directed against gliadin, and kits comprising antibodies, substrates on which such antibodies or peptide epitopes may be immobilized, or labeling reagents. The discovery that gliadin contains a diabetogenic epitope is not held to confer novelty on a claim directed to a known gliadin protein or gliadin-encoding nucleotide sequence (or its complement), as said epitope is held to be an inherent functional property thereof. Thus, the cited art anticipates those kits that comprise proteins comprising a diabetogenic epitope, a nucleotide sequence encoding such protein, or the complement of said nucleotide sequence. Consequently, the instant claims are considered to lack both novelty and an inventive step.

Claims 2, 7, 15, 16 and 23 meet the requirements of Articles 33(2) or 33(3) PCT for novelty and inventive step, as no combination of prior art appears to disclose or fairly suggest a diabetogenic epitope comprising the amino acid sequence EEQLRELRRQ, or a nucleotide sequence encoding said epitope.

With regard to industrial applicability:

Claims 1-25 meet the requirements of Article 33(4) PCR for industrial applicability.